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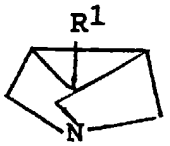
(54) Title: 4-AZATRICYCLO[2.2.1.0^{2,6}]HEPTANES AND PHARMACEUTICAL COMPOSITIONS



(I)

(I)

(57) Abstract

4-Azatricyclo[2.2.1.0^{2,6}]heptanes, formula (I) or salts or prodrugs thereof, where R' is an amide, ester, oxime ether or a 5-membered heterocycle and with a substituent of low lipophilicity, are useful in the treatment of neurological disorders and glaucoma. They may be prepared by methods of or analogous to published syntheses and may be formulated in conventional pharmaceutical compositions for administration.

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4-Azatricyclo[2.2.1.0^{2,6}]heptanes and pharmaceutical compositions.

The present invention relates to a class of substituted azatricyclic compounds which stimulate central muscarinic acetylcholine receptors and therefore are useful in the treatment of neurological and mental illnesses whose clinical manifestations are due to cholinergic deficiency. Such diseases include presenile and senile dementia (also known as Alzheimer's disease and senile dementia of the Alzheimer type respectively), Huntington's chorea, tardive dyskinesia, hyperkinesia, mania and Tourette Syndrome. Alzheimer's disease, the most common dementing illness, is a slowly progressive neurological disorder characterised by marked deficits in cognitive functions including memory, attention, language and visual perception capabilities.

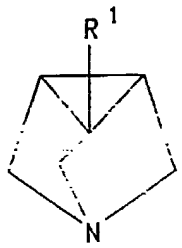
The compounds may also lower intraocular pressure and may therefore be used against glaucoma.

Published European Patent Application No. EPA-239309 discloses a class of oxadiaozle compounds having a first substituent of low lipophilicity, and an azacyclic or azabicyclic second substituent, which are useful in the treatment of neurodegenerative disorders. Published European Patent Application No. EPA-323,864 discloses a class of oxadiazoles having a first substituent selected from certain hydrocarbon groups and an azacyclic or azabicyclic substituent which also stimulate cholinergic transmission. There is no disclosure of azatricyclic structures in these specifications.

The compounds of the present invention are 4-azatricyclo[2.2.1.0^{2,6}]heptanes, or salts or prodrugs thereof, substituted on one of the ring carbon atoms thereof with an amide, ester, oxime ether, or an oxa- or

thia-diazole or an oxa- or thia-zole ring system which may itself be substituted on its other ring carbon atoms with a substituent of low lipophilicity or a hydrocarbon substituent.

Accordingly the present invention provides a compound of formula (I):



(I)

or a salt or prodrug thereof; wherein

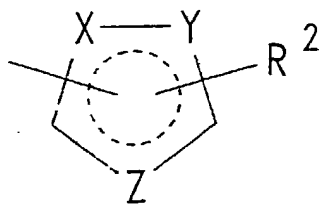
R^1 is $-COOR^3$, $-CONR^3R^4$, $-C(NR^5)R^6$;

wherein R^3 and R^4 are each independently C_{1-6} alkyl or taken together with the nitrogen to which they are attached may form a ring having up to 6 carbon atoms or R^4 may also be hydrogen;

R^5 is OA where A is C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, $OCOA_1$ where A_1 is hydrogen or A, or NHA_2 or NA_3A_4 where A_2, A_3 and A_4 are each independently C_{1-2} alkyl; and

R^6 is hydrogen or C_{1-4} alkyl provided that when R^5 is $OCOA_1$ or NHA_2 then R^6 is C_{1-4} alkyl;

or R^1 is a heterocyclic ring system selected from



wherein one of X,Y and Z represents an oxygen or sulphur atom and the remainder represent nitrogen atoms, or one of X and Y represents a nitrogen atom, the other of X and Y represents a carbon atom and Z represents an oxygen or sulphur atom, or one of X and Y represents an oxygen or sulphur atom, the other of X and Y represents a nitrogen atom and Z represents a carbon atom; and

R^2 represents hydrogen, halo, $-CF_3$, $-OR^7$, $-NR^7R^8$, -CN, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group; wherein R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; and R^8 is hydrogen or C_{1-6} alkyl.

Throughout this specification, unless otherwise stated, alkyl groups may be straight, branched or cyclic.

Preferred values for R^1 include (C_{1-6}alkoxy)-carbonyl such as methoxycarbonyl, $-CONR^3R^4$ such as when R^3 and R^4 taken together with the nitrogen atom form a ring such as a pyrrolidine ring or a (C_{1-3} alkyl)amide or di(C_{1-3} alkyl)amide such as n- or i-propylamide or N,N-diethylamide and $-C(NR^5)R^6$ wherein, in R^5, A and A_1 are selected from methyl, ethyl, allyl and propargyl, and A_2, A_3 and A_4 are methyl. Suitable values for R^5 include methoxy, ethoxy, allyloxy, propargyloxy, acetoxy and dimethylamino. When R^5 is -OA or $-NA_3A_4$, then R^6 is preferably hydrogen or methyl, and when R^5 is $-OCOA_1$ or $-NHA_2$, then R^6 is preferably methyl.

Examples of suitable ring systems for the group R^1 include the following: 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3-oxazole, 1,3-thiazole, isoxazole and isothiazole, preferably 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,3-oxazole or 1,3-thiazole. Especially preferred is 1,3-oxazole or 1,3-thiazole.

When the group R^2 is a hydrocarbon substituent, it may be C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl or aralkyl. The alkyl, alkenyl or alkynyl groups may be straight, branched or cyclic groups. Suitably the alkyl group comprises from 1 to 6 carbon atoms. The hydrocarbon group(s) may carry one or more substituents. Suitable substituent groups include halo, $-OR^7$, $-CF_3$ and $-SR^7$; wherein R^7 and R^8 are as defined with respect to formula (I) above.

Particular values of the group R^2 are hydrogen, hydroxy, chloro, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, amino, dimethylamino, methoxy, ethoxy, isopropoxy, n-butoxy, allyloxy and propargyloxy. Preferred values are n- or iso-propyl.

A suitable subgroup of compounds of formula (I) are those wherein R^1 is (C_{1-6} alkoxy)carbonyl such as methoxycarbonyl, $-CONR^3R^4$ such as pyrrolidine carboxamide or a heterocyclic ring such as 1,2,4-oxadiazole, 1,3-oxazole or isoxazole (and their corresponding thia-analogues); and, when R^1 is a heterocyclic ring, R^2 is hydrogen, C_{1-6} alkyl such as methyl or $-NR^7R^8$ such as $-NH_2$.

One group of prodrugs of compounds of this invention have a substituent on the heterocyclic ring R^1 which is hydrolysable <u>in vivo</u> to an amino group.

Groups which are hydrolysable <u>in vivo</u> to an amino group on the compounds of this invention may be readily ascertained by administering the compound to a human or animal and detecting, by conventional analytical techniques, the presence of the corresponding compound having an amino substituent in the urine of a human or animal. Examples of such groups include, for example, amido and urethane substituents, in particular a group of formula -NH.Q, wherein Q represents CHO, COR or CO_2R, and R represents an optionally substituted hydrocarbon group.

In this context, the hydrocarbon group R includes groups having up to 20 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable groups R include C_{1-9} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, and aryl(C_{1-6})alkyl. The alkyl group R may be straight or branched chain and may contain, for example, up to 12 carbon atoms, suitably from 1 to 6 carbon atoms. In particular the group may be substituted methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, n- or iso-heptyl, or n- or iso-octyl. Suitable cycloalkyl groups include cyclopentyl and cyclohexyl. The aryl group R includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, substituent groups.

Specific compounds within the scope of the present invention include the following, and salts and prodrugs thereof:

1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane;

1-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;

1-[5-(3-Amino-1,2,4-oxadiazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;

1-Carboxy-4-azatricyclo[2.2.1.$0^{2,6}$]heptane pyrrolidine amide;

1-(5-Oxazolyl)-4-azatricyclo[2.2.1.$0^{2,6}$]heptane;

1-[5-(3-Methylisoxazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;

Also included within the scope of the present invention are salts of the novel compounds. It will be appreciated that salts of the compounds for use in medicine will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful for the preparation of the compounds of the invention or their non-toxic pharmaceutically acceptable salts. Acid addition salts,

for example, may be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Where the novel compound carries a carboxylic acid group the invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Such quaternary ammonium derivatives penetrate poorly into the central nervous system and are therefore useful as peripherally selective muscarinic agents, useful for example as antispasmodic agents, agents to reduce gastric acid secretion, agents to block the muscarinic actions of acetylcholinesterase inhibitors in the treatment of myasthenia gravis and as agents to co-administer with muscarinic agonists in Alzheimer's disease. The method of treatment of this invention includes a method of treating Alzheimer's disease, senile dementia of the Alzheimer type, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania or Tourette syndrome by the administration to a patient in need of such treatment of an effective amount of one or more of the novel compounds.

This invention therefore also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier therefor.

It may, where appropriate, be advantageous, in order to reduce unwanted peripherally mediated side-effects, to incorporate into the composition a peripherally acting cholinergic antagonist (or anti-muscarinic agent).

Thus the compounds of the invention may advantageously be administered together with a peripheral cholinergic antagonist such as N-methylscopolamine, N-methylatropine, propantheline, methantheline or glycopyrrolate.

The compounds of the invention can be administered orally, parenterally or rectally at a daily dose of about 0.01 to 10 mg/kg of body weight, preferably about 0.1 to 1 mg/kg, and may be administered on a regimen of 1-4 times a day. When a cholinergic antagonist is administered, it is incorporated at its conventional dose.

The pharmaceutical formulations of this invention preferably are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills or capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the

advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspension include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

When administered for the treatment of elevated intraocular pressure or glaucoma, the active compound is preferably administered topically to the eye, although systemic treatment is, as indicated, also possible. The dose administered can be from as little as 0.1 to 25 mg or more per day, singly, or preferably on a 2 to 4 dose per day regimen althougn a single dose per day is satisfactory.

When given by the topical route, the active compound or an ophthalmologically acceptable salt thereof such as the hydrochloride salt is formulated into an ophthalmic preparation. In such formulations, from

0.0005% to 15% by weight can be employed. The objective is to administer a dose of from 0.1 to 1.0 mg per eye per day to the patient, with treatment continuing so long as the condition persists.

Thus, in an ophthalmic solution, insert, ointment or suspension for topical delivery, or a tablet, intramuscular or intravenous composition for systemic delivery, the active medicament or an equivalent amount of a salt thereof is employed, the remainder being carrier, excipients, preservatives and the like as are customarily used in such compositions.

The active drugs of this invention for use in treating glaucoma are suitably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as a suspension, ointment, or as a solid insert. A preferred composition is eye drops. Formulations of these compounds may contain from 0.0005 to 15% and especially 0.05% to 2% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the dose is effective in reducing or controlling elevated intraocular pressure. As a unit dosage from between 0.001 to 10.0 mg, preferably 0.005 to 2.0 mg, and especially 0.1 to 1.0 mg of the compound is generically applied to the human eye, generally on a daily basis in single or divided doses so long as the condition being treated exists.

This invention therefore further provides a pharmaceutical formulation adapted for topical administration to the eye which formulation comprises a compound of formula (I) and a carrier suitable for topical administration.

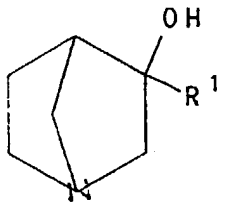
These hereinbefore described dosage values are believed accurate for human patients and are based on the known and presently understood pharmacology of the

compounds, and the action of other similar entities in the human eye. As with all medications, dosage requirements are variable and must be individualized on the basis of the disease and the response of the patient.

For topical administration, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like.

The pharmaceutical formulation may also be in the form of a solid insert such as one which after dispensing the drug remains essentially intact, or a bio-erodible insert that is soluble in lacrimal fluids or otherwise disintegrates.

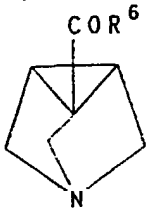
The compounds of this invention wherein R^1 is $-COOR^3$, $-CONR^3R^4$ or a heterocyclic ring system as defined may be prepared by cyclising a compound of formula (III) or an acid addition salt thereof:



(III)

wherein R^1 is $-COOR^3$, $-CONR^3R^4$ or a heterocyclic ring system as defined in formula (I). For example, cyclisation may be undertaken with diethylaminosulphur trifluoride by the method of A.M. MacLeod, R. Herbert and K. Hoogsteen, J. Chem. Soc. Chem. Commun., (1990), 100. The cyclisation may also be achieved using other reagents which generate a carbonium ion in the compound of formula (III) such as $SOCl_2$ or a strong acid eg trifluoroacetic acid.

The compounds of formula (I) wherein R^1 is $-C(NR^5)R^6$ may be prepared by reacting a compound of formula (IV)

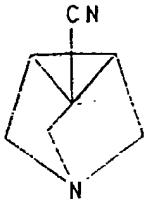


(IV)

wherein R^6 is as defined in formula (I) with a compound of formula $R^{5'}$-NH_2 (V) wherein $R^{5'}$ is R^5 as defined in formula (I) or hydroxy and thereafter, if necessary, converting $R^{5'}$ (when OH) to R^5.

The reaction between the compounds (IV) and (V) is preferably carried out in a hydroxylic solvent such as an alcohol such as methanol or ethanol either at ambient or elevated temperature. When R^5 in formula (I) is OA, NHA_1, or NA_1A_2, then $R^{5'}$ is preferably R^5. When R^5 in formula (I) is $OCOA_1$, then $R^{5'}$ is preferably hydroxy. Conversion of $R^{5'}$ (when OH) to R^5 may take place by conventional acylation methods, for example by treatment with a suitable acylating agent such as an acyl halide eg. acetyl chloride.

The compounds of formula (IV) may be prepared from the tricyclic nitrile of formula (VI):



(VI)

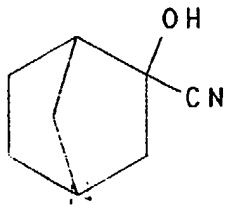
For example, by treating the compound (VI) with the corresponding alkyl lithium at depressed temperature, or

by treatment of a LiOOC group with an alkyl lithium, which LiOOC group itself can be obtained from a compound of formula (I) where R^1 is $-COOR^3$ with lithium hydroxide in water.

Alternatively, the compounds of formula (IV) may be prepared from the corresponding tricyclic chlorocarbonyl compound by reaction with N,O-dimethylhydroxylamine and an alkyl lithium.

Also to prepare compounds (I) where R^1 is $-COOR^3$ or $-CONR^3R^4$, the nitrile (VI) may be used as an intermediate and may be converted to an ester $-CO_2R^3$ or amide $-CONR^3R^4$ by conventional techniques.

The intermediates of formula (III) where R^1 is $-COOR^3$ or $-CONR^3R^4$ may likewise be prepared from the azabicyclic nitrile of formula (VII)



(VII)

by converting the cyano group by conventional techniques. Compounds (I) may then follow by cyclising the resulting compound of formula (III) as noted above. Alternatively, the intermediates of formula (VI) may be prepared from the compound of formula (VII) by cyclisation as described for the cyclisation of compounds (III) and then converted to compounds (I) by conventional techniques as noted above.

A compound of formula (VII) may be prepared by the method of C.J. Swain, C.O. Kneen and R. Baker, J. Chem. Soc. Perkin I., (1990), 3183.

A compound of formula (III) wherein R^1 is an oxazole or thiazole may be prepared by reaction of 1-azabicyclo-[2.2.1]heptan-3-one with a metal derivative of an oxazole or thiazole of formula (VIII)

wherein L represents oxygen or sulphur, R^2 is as defined in relation to formula (I) and M represents a metal atom, for example and alkali metal such as lithium. The lithium derivative may be prepared, for instance, by reacting the corresponding halo-substituted such as chloro-substituted oxazole or thiazole with n-butyl lithium.

Either before or after cyclisation, the compound of formula (III), where R^1 is a carboxylic ester $-CO_2R^3$ or nitrile of formula (VI) or (VII) may be converted to a heterocyclic ring system as defined for R^1 (eg. oxadiazole, thiadiazole, 1,3-oxazole, 1,3-thiazole, isoxazole or isothiazole) by conventional methods as described in standard textbooks on heterocyclic chemistry such as "Comprehensive Heterocyclic Chemistry", by A.R. Katritzky and C.W. Rees (Pergamon 1984), or in reviews on the subject such as "The Chemistry of Oxazoles" by I.J. Turchi and M.J.S. Dewar, in Synthesis, (1974), 389, or by methods analogous to those described in European patent specifications nos. EP-A-239,309 or EP-A-307,141.

For example, an oxazole may be prepared from a carboxylic ester by reaction with the anion of an isonitrile R^2CH_2NC. Suitable reagents for generating the

anion include lithium hexamethyldisilazide or lithium diisopropylamide in a solvent such as tetrahydrofuran or dimethoxyethane.

An isoxazole may be prepared by reacting a carboxylic ester with the anion of an oxime $CH_3C(NOH)R^2$ followed by heating in an acid such as sulphuric acid. The oxime anion may be formed using a strong base such as butyl lithium in a solvent such as tetrahydrofuran.

An oxadiazole may be prepared by reacting a carboxylic ester with an amide oxime $R^2(NOH)NH_2$ or a salt thereof in a solvent such as tetrahydrofuran, dimethyl formamide or a lower alkanol such as methanol, ethanol or propanol.

After any of the above-described processes are complete, one substituent R^2 can be converted to another. For example an amino group may be converted to chloro via the intermediacy of diazonium, $-N_2$. Similarly, a chloro substituent may be converted to methoxy by reaction with a nucleophile such as methoxide; alkoxycarbonyl groups may be converted, via carboxy, to an amino substituent, $-NH_2$; and methoxy may be converted to hydroxy by treatment with concentrated hydrobromic acid.

In any of the above reactions it may be necessary and/or desirable to protect any sensitive groups in the compounds. For example, if the reactants employed include amino, carboxy, keto, hydroxy or thiol groups, these may be protected in conventional manner. Thus, suitable protecting groups for hydroxy groups include silyl groups such as trimethylsilyl or t-butyldimethylsilyl, and etherifying groups such as tetrahydropyranyl; and for amino groups include benzyloxycarbonyl and t-butoxycarbonyl. Keto groups may be protected in the form of a ketal. Carboxy groups are preferably protected in a reduced form such as in the form of their corresponding protected

alcohols, which may be subsequently oxidised to give the desired carboxy group. Thiol groups may be protected by disulphide formation, either with the thiol itself or with another thiol to form a mixed disulphide. The protecting groups may be removed at any convenient stage in the synthesis of the desired compound according to conventional techniques.

The following Examples illustrate the preparation of compounds according to the invention. Each of the compounds of the Examples demonstrates an affinity for the muscarinic receptor, having an IC_{50} (concentration required to displace 50% of specific [^{3}H]-N-methylscopolamine binding from rat cortical membrane preparations) significantly lower than 100μM. Penetrability into the central nervous system of compounds of this invention was assessed by a measurable displacement of radioligand binding using standard "ex-vivo" binding techniques (Ref: J. Neurosurg., 1985, 63, 589-592).

In the Examples, all temperatures are in °C;

DESCRIPTION 1

1-Cyano-4-azatricyclo[2.2.1.$0^{2,6}$]heptane. To a suspension of 3-cyano-3-hydroxy-1-azabicyclo[2.2.1]heptane (2.7g) (prepared by the procedure described in the published European Patent Application EP 350118) in CH_2Cl_2 (50ml) was added diethylaminosulphur trifluoride (3.2ml) dropwise with stirring. After 30 minutes the solution was washed with $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The residue was treated with ethereal HCl and the resulting solid recrystallised from propan-2-ol to give the title compound as the hydrochloride salt (1.96g), mp 247°C (decomp.).

EXAMPLE 1

1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane

To a solution of 3-Carbomethoxy-3-hydroxy-1-azabicyclo[2.2.1]heptane (330mg) (prepared by the method of Swain *et al.*, J. Chem. Soc. Perkin I., (1990) 3183). in CH_2Cl_2 (10ml) at -78°C was added diethylamino sulphur trifluoride (0.3ml). The solution was warmed to room temperature then aqueous K_2CO_3 was added and extracted with CH_2Cl_2. The extract was dried with sodium sulphate and concentrated in vacuo to give a residue which was purified by chromatography on neutral alumina eluting with Et_2O. There was thus obtained the title compound (224mg) which was characterised as the hydrochloride salt, mp 205°C.

EXAMPLE 2

1-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-4-azatricyclo[2.2.1.$0^{2,6}$]heptane

Acetamide oxime (140mg) was stirred in tetrahydrofuran (10ml) with NaH (55% in oil, 80mg) and type 4A molecular sieves (0.5g) for 30 minutes. 1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane (183mg) in tetrahydrofuran (10ml) was added and the mixture heated under reflux for 1.5 hours. The reaction was allowed to cool and filtered then evaporated under reduced pressure. The residue was partitioned between aqueous K_2CO_3 and CH_2Cl_2 and the organic phase separated and dried with Na_2SO_4. The solution was concentrated and the residue crystallised from Et_2O/hexane to give the title compound (105mg) as white crystals, mp 75°C.

EXAMPLE 3

1-[5-(3-Amino-1,2,4-oxadiazol)-yl]-4-azatricyclo[2.2.1.$0^{2,6}$]heptane

Hydroxyguanidine sulphate (1.1g) was stirred in EtOH (20ml) with type 4A molecular sieves (2.5g) and sodium (371mg) for 16 hours. To this mixture was added 1-methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane hydrochloride (260mg). After heating under reflux for 5 hours the mixture was cooled, filtered

and concentrated in vacuo. The residue was dissolved in water and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), concentrated and the remaining solid triturated with Et_2O to give the title compound (55mg), mpt 216-217°C.

EXAMPLE 4

1-Oxo-1-pyrrolidinomethyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane Pyrrolidine Amide

1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane (350mg) was heated under reflux in pyrrolidine (3ml) for 12 hours. The mixture was evaporated under reduced pressure and the residue chromatographed on neutral alumina eluting with methanol/CH_2Cl_2 (1:99) to give the title compound as white needles (150mg), mp 89°C (Et_2O/hexane).

EXAMPLE 5

1-(5-oxazolyl)-4-azatricyclo[2.2.1.$0^{2,6}$]heptane. To a solution of methyl isocyanide (200µl) in tetrahydrofuran (5ml) at -78°C under an atmosphere of nitrogen was added lithium hexamethyldisylazide (4ml of a 1.0M solution in tetrahydrofuran). After 20 minutes 1-methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane (330mg) was added in tetrahydrofuran (2ml) and the solution allowed to warm to room temperature. After stirring for 4 hours, 5N NaOH solution was

added and the mixture extracted with Et_2O. The organic solution was dried with Na_2SO_4, concentrated and the residue purified by chromatography on alumina eluting with $MeOH/CH_2Cl_2$ (1:99) to give the title compound as a white crystalline solid, mp 72-73°C.

EXAMPLE 6

1-[5-(3-Methyl-isoxazol)-yl]-4-azatricyclo[2.2.1.$0^{2,6}$]heptane

Acetoneoxime (210mg) was dissolved in tetrahydrofuran (5ml) and cooled to 0°C under N_2. n-Butyllithium (3.6ml) was added and the solution stirred at 0°C for 1h. 1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane (350mg) in tetrahydrofuran (4ml) was then added dropwise and the reaction mixture stirred at 0°C for 1h. The solution was then warmed to room temperature and stirred for a further 16h. The reaction mixture was then poured into a rapidly stirred solution of 1.2g conc. H_2SO_4 diluted to 10ml with 4:1 tetrahydrofuran-water. The solution was refluxed for 1h, cooled and the phases separated. The aqueous layer was further extracted with dichloromethane and the organic extracts combined, dried and reduced to give an oil. The pure isoxazole was obtained by chromatography on alumina (grade III, 50% EtOAc/hexane) and characterised as the HCl salt, mp 208-210°C.

PHARMACEUTICAL EXAMPLES

1. Tablets containing 1 - 25 mg of a compound of formula (I)

	Amount - mg		
Compound (I)	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

2. Tablets containing 26 - 100 mg of a compound of formula (I)

	Amount - mg		
Compound (I)	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

Compound (I), lactose, and a portion of the corn starch are mixed together and granulated to a 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0 mg, 2.0 mg, 25.0 mg, 26.0 mg, 50.0 mg and 100.0 mg of compound (I) per tablet.

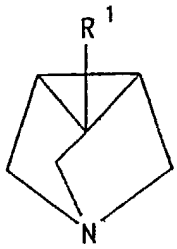
3. Eye Drops

The pharmaceutically acceptable salt of the active compound	0.5%
Benzalkonium chloride solution	0.02% v/v
Disodium edetate	0.05%
NaCl	0.8%
Water for injections	to 100%

The formulation is sterilised by autoclaving.

CLAIMS

1. A compound of formula (I)



(I)

or a salt or prodrug thereof; wherein

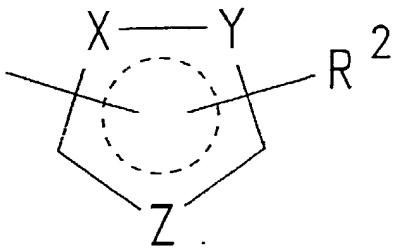
R^1 is $-COOR^3$, $-CONR^3R^4$, $-C(NR^5)R^6$;

wherein R^3 and R^4 are each independently C_{1-6} alkyl or taken together with the nitrogen to which they are attached may form a ring having up to 6 carbon atoms or R^4 may also be hydrogen;

R^5 is OA where A is C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, $OCOA_1$ where A_1 is hydrogen or A, or NHA_2 or NA_3A_4 where A_2, A_3 and A_4 are each independently C_{1-2} alkyl; and

R^6 is hydrogen or C_{1-4} alkyl provided that when R^5 is $OCOA_1$ or NHA_2 then R^6 is C_{1-4} alkyl;

or R^1 is a heterocyclic ring system selected from



wherein one of X,Y and Z represents an oxygen or sulphur atom and the remainder represent nitrogen atoms, or one

of X and Y represents a nitrogen atom, the other of X and Y represents a carbon atom and Z represents an oxygen or sulphur atom, or one of X and Y represents an oxygen or sulphur atom, the other of X and Y represents a nitrogen atom and Z represents a carbon atom; and

R^2 represents hydrogen, halo, $-CF_3$, $-OR^7$, $-NR^7R^8$, -CN, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group; wherein R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; and R^8 is hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 wherein R^1 is (C_{1-6}alkoxy)carbonyl such as methoxycarbonyl, $-CONR^3R^4$ such as when R^3 and R^4 taken together with the nitrogen atom form a ring such as a pyrrolidine ring or a (C_{1-3} alkyl)amide or di(C_{1-3} alkyl)amide such as n- or i-propylamide or N,N-diethylamide and $-C(NR^5)R^6$ wherein, in R^5, A and A_1 are selected from methyl, ethyl, allyl and propargyl, and A_2, A_3 and A_4 are methyl.

3. A compound according to claim 1 wherein R^1 is 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3-oxazole, 1,3-thiazole, isoxazole or isothiazole.

4. A compound according to claim 3 wherein R^2 is hydrogen, hydroxy, chloro, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, amino, dimethylamino, methoxy, ethoxy, isopropoxy, n-butoxy, allyloxy or propargyloxy.

5. A compound according to claim 2 wherein R^1 is (C_{1-6} alkoxy)carbonyl such as methoxycarbonyl, $-CONR^3R^4$ such as pyrrolidine carboxamide or a heterocyclic ring such as 1,2,4-oxadiazole, 1,3-oxazole or isoxazole

(and their corresponding thia-analogues); and, when R^1 is a heterocyclic ring, R^2 is hydrogen, C_{1-6} alkyl such as methyl or $-NR^7R^8$ such as $-NH_2$.

6. A compound according to claim 1 selected from the group consisting of
1-Methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane;
1-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;
1-[5-(3-Amino-1,2,4-oxadiazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;
1-Carboxy-4-azatricyclo[2.2.1.$0^{2,6}$]heptane pyrrolidine amide;
1-(5-Oxazolyl)-4-azatricyclo[2.2.1.$0^{2,6}$]heptane;
1-[5-(3-Methylisoxazol)-yl]-4-azatricyclo-[2.2.1.$0^{2,6}$]heptane;

and salts and prodrugs thereof.

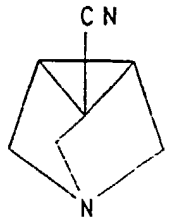
7. A pharmaceutical formulation comprising a compound according to any of claims 1 to 6 and a pharmaceutically acceptable carrier therefor.

8. A formulation according to claim 7 in a form suitable for oral, parenteral or topical administration.

9. A method of treating a neurological disorder or glaucoma which method comprises the administration to a patient in need thereof of a pharmacologically effective amount of a compound of formula (I) or salt or prodrug thereof.

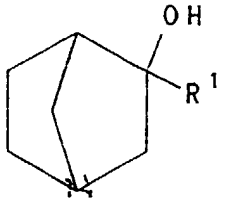
10. The use in medicine of a compound of formula (I) or a salt or prodrug thereof for the treatment of a neurological disorder or glaucoma.

11. A compound of formula (VI)



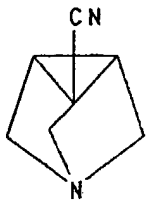
(VI)

12. A process for the preparation of a compound according to claim 1, which process comprises:
(a) when R^1 is $-COOR^3$, $-CONR^3R^4$ or a heterocyclic ring system as defined, cyclising a compound of formula (III) or an acid addition salt thereof:



(III)

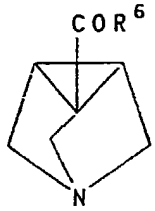
wherein R^1 is $-COOR^3$, $-CONR^3R^4$ or a heterocyclic ring system as defined in formula (I); or
(b) by converting by standard methods the tricyclic nitrile of formula (VI):



(VI)

or

(c) when R^1 is $-C(NR^5)R^6$, reacting a compound of formula (IV)



(IV)

wherein R^6 is as defined in formula (I) with a compound of formula $R^{5'}-NH_2$ (V) wherein $R^{5'}$ is R^5 as defined in formula (I) or hydroxy and thereafter, if necessary, converting $R^{5'}$ (when OH) to R^5;
and thereafter, if necessary, converting any compound of formula (I) so prepared to any other compound of formula (I) or to a salt or prodrug thereof.

13. A compound of formula (I) when prepared by a process according to claim 12.

14. A compound, formulation or process substantially as hereinbefore described with reference to the description or examples.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/02016

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC C 07 D 487/08, IPC[5]: A 61 K 31/40, 31/41, 31/42 //(C 07 D 487/08, 209:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 487/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0366304 (BEECHAM) 2 May 1990 see claim 1; examples 5,6,17; page 3, lines 14-16	1,10
A	EP, A, 0392803 (BEECHAM) 17 October 1990 see claim 1; examples 9,11-14,16-28; page 3, lines 6-8	1,10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th July 1991	23 AUG 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body by means of surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9002016

SA 43406

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 16/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0366304	02-05-90	AU-A- 4278289	26-04-90
		JP-A- 2134380	23-05-90
EP-A- 0392803	17-10-90	AU-A- 5315990	18-10-90
		JP-A- 3007285	14-01-91